ORIGINAL ARTICLE INFECTIOUS DISEASES

Community-acquired pneumonia in immunocompromised older patients: incidence, causative organisms and outcome

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Abstract

The number of elderly patients in the community with immunosuppressive conditions has increased progressively over recent decades. We sought to determine the incidence, causative organisms and outcome of community-acquired pneumonia (CAP) occurring in immunocompromised older patients. We prospectively compared cases of CAP in immunocompromised and non-immunocompromised patients admitted to five public hospitals in three Spanish regions. Of 320 cases studied, 115 (36%) occurred in immunocompromised patients, including: solid or hematological malignancy (97), corticosteroids or other immunosuppressive drugs (44), solid organ or stem cell transplant (five), and other conditions (eight). The etiology was established in 44% of immunocompromised patients vs. 32% of non-immunocompromised patients (p 0.03). *Streptococcus pneumoniae* was the most common causative organism in both groups (29% vs. 21%; p 0.08), followed by *Legionella pneumophila* (3% vs. 6%; p 0.01). Gram-negative bacilli were more frequent among immunocompromised patients (5% vs. 0.5%; p <0.01), particularly *Pseudomonas aeruginosa* (3% vs. 0%; p 0.04). Nocardiosis was only observed in immunocompromised patients (two cases). Bacteremia occurred similarly in the two groups. No significant differences were found with respect to ICU admission (8%, in both groups) or the length of stay (12.5 vs. 10.4 days). The early (<48 h) (3.5 vs. 0.5%; p 0.04) and overall case-fatality rates (12% vs. 3%; p <0.01) were higher in immunocompromised patients. In conclusion, a substantial number of older patients hospitalized for CAP are immunocompromised. Although relatively uncommon, CAP due to gram-negative bacilli, including *P. aeruginosa*, is more frequent among these patients. CAP occurring in immunocompromised patients causes significant morbidity and mortality.

Keywords: CAP, community-acquired pneumonia, elderly, immunocompromised, immunosuppression
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Introduction

Community-acquired pneumonia (CAP) is the third-most-frequent hospital diagnosis among patients aged ≥65 years and the sixth leading cause of death in developed countries. In Spain, the incidence of CAP in adults is 2–10 cases/1000 inhabitants/year; but increases to 25–35 cases/1000 inhabitants in people aged >70 years. At least 20% of patients with CAP require hospitalization. The mortality is 10–25%, and is particularly high in the elderly [1] and patients requiring intensive care unit (ICU) admission [2].

The number of elderly patients in the community with immunosuppressive conditions has increased progressively over recent decades [3]. Even though the clinical aspects of nosocomial pneumonia in immunosuppressed patients are well documented, there are few studies of CAP in patients

aged ≥65 years. Moreover, immunocompromised patients have been systematically excluded from prospective CAP studies. In addition, the Infectious Diseases Society of America and the American Thoracic Society consensus guidelines on the management of CAP in adults do not include recommendations for immunocompromised patients [4].

We sought to determine the incidence, causative organisms and outcome of CAP in immunocompromised older patients.

Methods

Setting, participants, and study design

A prospective, observational, multicenter study was conducted in patients aged ≥65 years hospitalized with CAP through the emergency departments of five public hospitals (providing universal free care to the whole population) in three Spanish regions (Aragon, Catalonia, and Galicia) between May 1, 2005 and January 31, 2007. Exclusion criteria were permanent nursing home residence, patients with nosocomial pneumonia (onset ≥2 days after hospital admission), patients whose initial diagnosis of pneumonia was not confirmed during the hospital stay, and CAP due to fungal or mycobacterial etiology.

We compared causative organisms and outcomes in cases of CAP in immunocompromised and non-immunocompromised patients. Outcomes variables analyzed were ICU admission, length of stay, and early and overall case-fatality rates. The ethics committee of each participating hospital approved the study. Oral consent was obtained from all participants or a close relative.

Clinical assessment, antibiotic therapy, and follow-up

At the initial visit, before starting empirical antibiotic therapy, participants underwent a complete clinical history and physical examination. Basic chemistry and hematologic tests, arterial blood gas determinations, and chest radiography were performed. There was not an established protocol for microbiological work up in the study. The microbiological tests were those routinely used in clinical practice at each center. Microbiological studies mainly included two sets of blood cultures and sputum Gram stain and culture when available. Urinary antigen detection for *S. pneumoniae* was performed as indicated by attending physician. Participants were stratified into risk classes and the validated prediction rule calculated according to the Pneumonia Severity Index (PSI) score, as previously described [5].

Empirical antibiotic therapy was administered according to individual hospital guidelines. One or more study investigators saw participants daily during their hospital stay and recorded clinical and microbiological data. The investigators made no decisions about ICU admission or hospital discharge, which were always made by attending physicians. A long-term follow-up visit was made *c.* 1 month after hospital discharge. All assessments were made using a standard protocol form with a checklist of items.

Definitions

Hospitalization criteria have been previously described [6]. Pneumonia was defined as a new infiltrate on chest X-ray and one or more of the following symptoms or signs of acute lower respiratory tract infection: cough, chest pain, fever >38°C, temperature <35°C, and dyspnea within the previous 24 h [7]. Immunosuppression was considered to be present when ≥1 of the following conditions were documented: underlying solid or hematological malignancy, solid organ or stem cell transplant, seropositivity for human immunodeficiency virus (HIV), splenectomy, radiotherapy, administration of corticosteroids (≥20 mg/day during 2 weeks in the last month) and other immunosuppressive drugs, and congenital or acquired immune deficiency disorder. The immunocompromised state had to be active at the time of patient's inclusion. A neoplastic disease was defined as active if it required medical or surgical intervention within the last year or if no-treatable metastases were present at time of the inclusion into the study. Radiotherapy was considered within the last 3 months and chemotherapy or corticosteroids within 1 month.

Length of stay (LOS) was measured in days and was calculated as the time from admission to the date of hospital discharge. The early case fatality-rate was defined as death from any cause ≤48 h after hospitalization. The overall case-fatality rate was defined as death from any cause within 30 days of hospitalization.

Microbiological studies

Pathogens in blood, normally sterile fluids, sputum and other samples were investigated using standard microbiological procedures. Isolation of *Legionella* was attempted in sputum and other respiratory samples by using selective media (buffered charcoal-yeast extract agar). *S. pneumoniae* antigen in urine was detected using rapid immunochromatography (NOW assay, Binax, Inc., Portland, ME, USA). *L. pneumophila* serogroup 1 antigen in urine was detected using immunochromatography (NOW *Legionella* Urinary Antigen, Binax, Inc.). Standard serological methods were used to determine antibodies against the following pathogens: *Mycoplasma pneumoniae* (indirect agglutination), *Chlamydia psittaci* [immunofluorescence (IF)], *Chlamydia pneumoniae* (micro-IF), *Coxiella*

burnetii (IF), and *L. pneumophila* (serogroups 1–6) [enzyme immunoassay (EIA)]. Four-fold rises in the titer of IgG antibodies or detection of IgM antibodies or both were considered diagnostic.

Statistical analysis

Outcome variables were compared in immunocompromised and non-immunocompromised patients. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed by non-parametric tests after verifying a non-normal distribution. All statistical tests were two-tailed and $p < 0.05$ was deemed significant. The analysis was made using the SPSS v17.0 (SPSS Inc., Chicago, IL, USA) statistical package.

Results

A total of 320 patients aged ≥65 years hospitalized with CAP were studied, 115 (36%) of whom were immunocompromised and 205 (64%) non-immunocompromised.

Patients' clinical and microbiological characteristics are shown in Table 1. The underlying immunosuppressive conditions were ≥1 of the following: solid or hematological malignancy in 97 patients, pharmacologic immunosuppression (corticosteroids or cytostatic drugs) in 44, solid organ or stem cell transplant in five and other conditions in eight. There were no HIV-infected patients. Of 26 patients considered to be immunocompromised to corticosteroid therapy, only 9 (34.6%) had chronic obstructive pulmonary disease. Immunocompromised patients were mainly male and had a younger mean age than non-immunocompromised patients. There were more cases of previous pneumonia in immunocompromised patients. No difference was observed in the frequency of previous pneumococcal and seasonal influenza vaccination. The mean duration of symptoms before hospitalization in immunocompromised and non-immunocompromised patients was 4.9 ± 6 vs. 5.1 ± 4.3 days, respectively (p 0.73). Immunocompromised patients were more often classified into the PSI high risk classes.

An etiologic diagnosis was made in 116 (36.3%) patients: 50 (44%) were immunocompromised and 66 (32%) non-immunocompromised (p 0.03). Blood cultures were obtained more often in immunocompromised patients. Bacteremia was detected in 14 (12.2%) immunocompromised and 19 (9.3%) non-immunocompromised patients (p 0.41).

TABLE 1. Clinical and microbiological characteristics of cap in immunocompromised and non-immunocompromised patients

Variable *n* (%)	Immunocompromised patients (*n* = 115)	Non-immunocompromised patients (*n* = 205)	p
Sex (male)	83 (72.2)	110 (53.7)	<0.01
Mean age (years)	75.2 ± 6.5	77.5 ± 7.8	<0.01
Previous pneumonia	28 (25.2)	32 (16.2)	0.05
Pneumococcal vaccine	55 (47.8)	81 (39.5)	0.15
Seasonal influenza vaccine	66 (57.4)	121 (59.0)	0.78
Current smoker	49 (7.9)	16 (7.8)	0.96
Former smokers	45 (47.0)	73 (35.6)	0.05
Alcohol abuse	7 (7.6)	19 (10.4)	0.45
PSI risk classes[a]			<0.01
II	0 (0)	27 (13.2)	
III	19 (16.5)	69 (33.7)	
IV	52 (45.2)	76 (37.1)	
V	31 (27)	15 (7.3)	
Causative agents			
S. pneumoniae	33 (28.7)	43 (20.9)	0.08
H. influenzae	2 (1.7)	2 (0.98)	0.45
L. pneumophila	3 (2.6)	12 (5.8)	0.15
P. aeruginosa	3 (2.6)	0 (0)	0.04
Nocardia spp.	2 (1.7)	0 (0)	0.13
Gram-negative bacilli	6 (5.2)	1 (0.5)	0.01
Atypical and *Legionella* spp	4 (3.5)	16 (7.8)	0.09
Unknown etiology	65 (56.5)	139 (67.8)	0.03
Diagnostic methods			
Blood cultures	87 (76.3)	119(58)	<0.01
Sputum culture	39 (33.9)	73 (35.6)	0.76
Sputum culture +	15 (38.5)	13 (17.8)	0.02
Legionella antigen	68 (59.1)	152 (74.1)	<0.01
Legionella antigen +	3 (4.4)	12 (7.9)	0.40
Pneumococcal antigen	86 (74.8)	171 (83.4)	0.06
Pneumococcal antigen +	27 (31.4)	31 (18.1)	0.01
Invasive procedures	7 (6.09)	16 (7.80)	0.57
Fibrobronchial aspirate	2 (1.74)	2 (0.97)	
Protected specimen brush	1 (0.87)	0 (0)	
Bronchoalveolar lavage	2 (1.74)	1 (0.49)	
Pleurocentesis	2 (1.74)	12 (5.85)	
Transthoracic needle aspiration	0 (0)	1 (0.49)	

[a]PSI scores were missing in 13 immunocompromised patients and in 18 non-immunocompromised patients

An etiologic diagnosis was made by bronchoscopy (including fibrobronchial aspirate, protected specimen brush, and bronchoalveolar lavage) in 5 (4.3%) immunocompromised and 3 (1.4%) non-immunocompromised episodes.

The most-frequent microorganisms causing CAP were *S. pneumoniae* (76, 65.6%), *L. pneumophila* (15, 12.9%) and *H. influenzae* (4, 3.5%), with no differences between groups. Gram-negative bacilli were isolated more often in immunocompromised patients (5.2% vs 0.5%; p 0.01). *P. aeruginosa* and *Nocardia spp.* were isolated only in immunocompromised patients (three and two, respectively). There was one case of *Staphylococcus aureus* pneumonia and viral pneumonia due to respiratory syncytial virus, respectively, both in immunocompromised patients.

Table 2 shows the empirical antimicrobial therapy and outcomes of CAP in the two groups. Most patients were given initial antibiotic monotherapy (70; 60.9% vs. 127; 62%). Levofloxacin was the most-frequently administered drug in both groups (29; 25.2% vs. 64; 31.2%). The mean number of treatment days was 13.6 vs. 12.8 days, respectively (p 0.36). The frequency of ICU admission, mechanical ventilation and the length of hospital stay did not differ between groups.

The early (<48 h) (3.5% vs. 0.5%; p 0.04) and overall case-fatality rates were higher in immunocompromised patients (12% vs. 3%; p <0.01). All three cases of pneumonia caused by *P. aeruginosa* were complicated by bacteremia, resulting in two deaths.

Discussion

A substantial number of elderly patients hospitalized for CAP in the present study were immunocompromised due to various underlying conditions. This probably reflects a change in our indwelling population, with larger numbers of older immunocompromised patients, due mainly to transplantation, malignancy, corticosteroids and other immunosuppressive drugs. In a recent population-based study of CAP in older adults [3], the incidence rate of CAP was almost three-fold higher among immunocompromised patients than in immunocompetent subjects. A case-control study investigating the risk of hospitalization for pneumonia in older adults in Canada found that the use of immunosuppressant medication was an important risk factor for CAP, with an OR = 15.13 (95% CI, 4.7–48.3; p <0.05) in the multivariate analysis [8].

The impact of the immune status in CAP has been little studied [9–13]. A prospective 1-year study by Mundy *et al.* in 1990 evaluated the immune status of hospitalized patients with CAP. Concurrent immunosuppression was observed in 57% of the 221 patients, 180 of whom were HIV-infected. These results are consistent with the disproportionate impact of HIV-infection on admissions for CAP two decades ago, compared with other conditions. Although there has been a substantial decline in the number of HIV-infected patients admitted to hospital due to CAP over the last 15 years, the older age the patients in our study may explain, in part, the absence of HIV-infections.

An etiological diagnosis was made in a relatively-low proportion of our patients compared with other recent studies [1]. The rate of identification of a causative agent of CAP in clinical practice is low and the etiology may remain obscure in more than half of all cases [14]. A multicenter study in the USA that assessed routine clinical practice in cases of CAP found that the cause was identified in only 25% of cases [15]. Some studies have reported even-lower diagnostic rates in the elderly, with identification of causative organisms in 5–20% of CAP cases [16,17], perhaps indicating a reluctance to perform invasive procedures in this age-group.

The distribution of microorganisms was essentially the same in immunocompromised and non-immunocompromised patients. As expected [18], *S. pneumoniae*, which is the most frequent cause of CAP in a wide variety of immunocompro-

TABLE 2. Comparison of empirical antimicrobial therapy and clinical outcomes in immunocompromised and non-immunocompromised patients with CAP

Variable	Immunocompromised patients (*n* = 115)	Non-immunocompromised patients (*n* = 205)	p
Antibiotic monotherapy *n* (%)	70 (60.9)	127 (62.0)	0.94
Levofloxacin	29 (25.2)	64 (31.2)	0.31
Amoxicillin-clavulanate	10 (8.7)	47 (22.9)	<0.01
Ceftriaxone	15 (13.0)	12 (5.9)	0.03
Piperacillin-tazobactam	6(5.2)	0(0)	<0.01
Combination therapy *n* (%)			
Ceftriaxone + levofloxacin	21 (18.3)	36 (17.6)	0.88
Ceftriaxone + azithromycin	5 (4.3)	25 (12.2)	0.02
Amoxicillin-clavulanate + azithromycin	1 (0.9)	9 (4.4)	0.08
ICU admission *n* (%)	9 (7.8)	16 (7.8)	0.99
Mechanical ventilation *n* (%)	6 (5.2)	6 (2.9)	0.30
Bacteremia *n* (%)	14(12.2)	19(9.3)	0.41
Pleural effusion *n* (%)	2 (1.7)	10 (4.9)	0.16
Length of stay (days)	12.5 ± 12.2	10.4 ± 10.1	0.10
Early mortality (≤48 h) *n* (%)	4 (3.5)	1 (0.5)	0.04
Overall mortality *n* (%)	14 (12.2)	7 (3.4)	<0.01

mised patients, was the most-common etiological agent, independently of the immune status [11,12,19–22].

Pseudomonas aeruginosa pneumonia occurs rarely, if at all, in non-immunocompromised patients. In a large, prospective, population-based study of 5130 patients in the German Competence Network for Community-Acquired Pneumonia (CAPNETZ study) [23], the incidence of *Enterobacteriaceae* and *P. aeruginosa* in patients with CAP was 1.3% and 0.4%, respectively. In our study, gram-negative bacilli were significantly more-frequent in immunocompromised than in non-immunocompromised patients and CAP due to *P. aeruginosa* occurred only among immunocompromised patients.

Staphylococcus aureus, and particularly methicillin-resistant strains, are a challenge in most hospitals and a growing cause for concern in community-onset pneumonia in the United States [24–26]. The lack of virus detection in our patients may be explained by the lack of routine investigation of respiratory viruses. In a recent Spanish study [11] specifically addressing the incidence of viral CAP in immunocompromised patients, which required a nasopharyngeal swab for respiratory viruses, an etiologic diagnosis was made in 66% of cases and the most-frequent pathogen detected was *S. pneumoniae* (48%), followed by rhinovirus (18%).

A recent study [27] found a substantial reduction in mortality among elderly patients with CAP between 1987 and 2005. The authors suggested that a large part of this reduction is explained by increased vaccination rates and the use of guideline-concordant antibiotics. The poorer prognosis observed in our immunocompromised patients could be related to greater disease severity, as demonstrated by the PSI risk class at admission, different etiological agents and the host's suppressed immune response. In the CAPNETZ study [23], 30-day mortality was significantly higher in patients with pneumonia caused by *Enterobacteriaceae* and *P. aeruginosa*. A study [13] analyzing the utility of PSI in immunocompromised patients admitted for CAP, found an overall mortality rate of 14%. Patients with HIV-infection, solid organ transplantation or treatment with immunosuppressive drugs had an in-hospital mortality of 4.3%, whereas patients with hematological malignancies, chemotherapy, chest radiation or bone marrow transplantation had a rate of 20%.

Our study has some limitations. Conventional microbiological tests were not performed in all patients. Moreover, information on the proportion of fungal or mycobacterial CAP was not available. However, we think that tuberculosis and fungal infections represent two distinctive clinical settings. The appropriateness of empirical therapy could not be evaluated in all centers and the influence of empirical therapy on the outcome could not therefore be established. Finally, our results are limited to cases that required hospitalization and may not be applicable to cases treated as outpatients.

In conclusion, our study shows that a substantial number of older patients hospitalized for CAP are immunocompromised. Although relatively uncommon, CAP due to gram-negative bacilli, including *P. aeruginosa*, is more frequent among these patients. CAP occurring in immunocompromised patients causes significant morbidity and case-fatality rates.

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Transparency Declaration

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